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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/672,280
Filing Date: September 26, 2003
Appellant(s): LAZAR ET AL.

Robin M Silva
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed on February 16, 2010 appealing from the Office action mailed April 13, 2009.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of the claims contained in the Brief is correct.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief except that the new Information Disclosure Statement (IDS) and Supplemental IDS with Statement of Relatedness (both filed on May 17, 2010) submitted after the filing of the Appeal (on February 16, 2010) have not been considered because the IDSs containing new evidence were not filed timely before the filing of an Appeal Brief. See 37 CFR 41.33(d)(2).

Further, the IDSs filed were not accompanied with a statement according to 37 CFR 1.97(e). See MPEP 609.

Since evidence contained in the IDSs submitted after the filing of an Appeal Brief is not permitted under 37 CFR 41.33(d)(2), and since the IDSs filed were not accompanied with a statement according to 37 CFR 1.97(e), the IDSs have been placed in the file but have not been considered by the Office.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the Grounds of Rejection to be Review on Appeal is substantially correct, except for following:

A) The following provisional obviousness-type double patenting rejections have been withdrawn

Since the copending USSN 11/765,402 is abandoned, the provisional obviousness-type double patenting rejection against the claims of this copending application has been rendered moot.

Further, given that the copending claims of the USSNs 11/538,406, 11/766,609, and 11/764,001 have been amended such that there is no overlapping subject matter with the instant claims, the provisional obviousness-type double patenting rejections against the claims of these copending applications have been withdrawn.

Furthermore, given that there have been multiple amendments to the claims for the large number of applications that have been cited for provisional obviousness-type double patenting rejection, the status of such copending claims have been updated as of May 27, 2010.

B) On page 40 of the Brief under Section B, appellant states

"B. Claims 89, 91, 92, 94, 95, 96, 97, 98-102 ('in part), 106-112 ('in part), 135, 136, 140, 141, and 142-144 ('in part)

Claims 89, 91, 92, 94, 95, 96, 97, 98-102 (in part), 106-112 (inpart), 135, 136, 140, 141, and 142-144 (in part) are finally rejected under 35 USC 103(a) over Presta, US Patent 6,737,056."

This is not consistent with the rejection of record wherein claims 91, 92, 94-102, 107 and 110 have been withdrawn and therefore have not been rejected.

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief, except for the typographical error in claim 112. Once again, claim 112 contains a typographical error of "any of claims 88-9392" (see page 3-4 of the Office Action mailed on April 13, 2009). As stated in the office action of April 13, 2009 (paragraph #8, for examination purposes, claim 112 has been considered as dependent on claim 88. Appellant still has not corrected this error.

(8) Evidence Relied Upon

US 6,737,056 Presta 05-2004

Given that the instant claims are subjected to provisional obviousness-type double patenting rejections, the following copending applications upon which the rejections are based have been listed herein.

USSN 11/124,620, filed on May 5, 2005,

USSN 11/396,495, filed on March 31, 2006,

USSN 11/538,411, filed on October 3, 2006,

USSN 11/544,165, filed on October 6, 2006,

USSN 11/618,457, filed on December 29, 2006,

USSN 11/618,472, filed on December 29, 2006,

USSN 11/618,488, filed on December 29, 2006,

USSN 11/765,353, filed on June 19, 2007,

USSN 11/765,390, filed on June 19, 2007,

USSN 11/766,609, filed on June 21, 2007.

(9) Grounds of Rejection

The following grounds of rejection are applicable to the appealed claims:

Claims 88, 89, 103-106, 108, 109, 111, 112, 135-137, 139, 140, 142, and 144 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Presta (US Patent 6,737,056. Reference A97 on IDS) for reasons of record.

Presta teaches and claims an antibody including (monoclonal antibody or humanized) or immunoadhesin, wherein the antibody or immunoadhesin comprises a variant Fc region wherein the Fc region comprises amino acid substitution at position 239, wherein the antibody or immunoadhesin exhibits increased binding to FcγRs (e.g. see columns 13, 14, 35, and 36). Presta teaches that the binding sites of human and murine antibodies for FcγRs have been mapped to residues 233-239 (e.g. see second paragraph on column 3 and claim 13).

Further, Presta teaches that the preferred molecular targets of the variants include antibodies against CD20 (see 2nd paragraph of column 30, in particular) and said antibody or immunoadhesin can be formulated into a composition comprising a pharmaceutically acceptable carrier (e.g. see column 42).

Given that the antibody or immunoadhesin taught by Presta comprises the same structure of an amino acid substitution at position 239 of the Fc region and function of increased binding to an FcγR as the claimed invention, it would have been inherent/intrinsic properties of the prior art antibody or immunoadhesin to have increased binding to FcγRIIIa for allotype of V158 or F158.

The prior art teachings differ from the claimed invention by not exemplifying amino acids substitutions S239D, S239E, S239Q, and S239T [pre-existing serine (S) in position 239 substituted with aspartic acid (D), S239E glutamic acid (E), S239Q glutamine (Q), or S239T threonine (T)].

However, the key invention of Presta is that it identifies position 239 of the Fc region can be substituted with any other naturally occurring amino acid residues including D, E, Q or T for increased binding to Fc gamma receptor and therefore enhanced ADCC effect (e.g. see column 12 and paragraphs between Tables in column 20 and claim 13). Presta further provides working examples of method of making Fc variant comprising amino acid substitution in position 239 and methods of determining the variant's binding affinity to Fc gamma receptors (e.g. see Example 4 on columns 54-58 and Table 6 on columns 57-58).

Given that Presta identifies that position 239 of the Fc region can be substituted with any other naturally occurring amino acid residues for increased binding affinity to an Fcγ receptor, one of skill in the art would choose from this finite number of identified residues with a reasonable expectation of success absent any objective evidence of unexpected results.

Since the prior art teaches and claims that position 239 of the Fc region can be substituted for improved binding affinity to an Fcγ receptor and enhanced ADCC function and provides multiple working examples of amino acids substitutions using naturally occurring amino acid residues in the Fc region, it would have been obvious to one of skill in the art at the time of the invention to achieve the predictable results of enhancement of ADCC by making S239D in the Fc region of an antibody or immunoadhesin.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 88, 89, 103-106, 108, 109, 111, 112, 135-137, 139, 140, 142, and 144 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over the following copending applications for reasons of record:

The copending claims listed herein have been updated to the most currently filed claims.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both the instant and the copending application claims are drawn to same or nearly the same polypeptide variants with the same modifications to the Fc region at position 239 including 239D, 239E, 239Q, or 239T for altered affinity for FcγRs and effector functions. Given that the protein comprising an Fc variant relies on the same or nearly the same amino acid modification, the copending claims would anticipate the instant claims.

Claims 42 and 43 (amended claims filed 01/15/2010) of copending USSN11/124,620, drawn to a protein (defined as antibody in paragraphs, e.g. [91] and [102] of the specification of the '620 application) comprising an Fc variant of a parent Fc polypeptide comprising amino acid modifications including 239D.

Claims 1-6, 9, 12, 19, 21, and 23 (amended claims filed 09/04/2009) of copending USSN 11/396,495, drawn to an Fc variant of a parent Fc polypeptide comprising amino acid modification 239D wherein the Fc variant can be human IgG1 antibody (e.g. see copending claim 1-3),

Claims 1-5, 8-17, 20, and 21 (amended claims filed 04/07/2010) of copending USSN 11/538,411, drawn to a protein comprising an Fc variant of a parent Fc polypeptide wherein the Fc variant comprises amino acid substitution in position 239 including 239D and wherein the protein is defined as antibody in the copending specification (e.g. see paragraphs [68], [70], and [75]),

Claims 1, 4, 11, 12, 15-17, and 20-24 (amended claims filed 12/18/2009) of copending USSN 11/544,165, drawn to an anti-CD30 antibody comprising amino acid substitution 239D in the Fc region,

Claims 37, 38, and 44 (amended claims filed 05/17/2010) of copending USSN 11/618,457, drawn to an anti-CD20 antibody comprising an Fc variant comprising modification 239D in the Fc region,

Claims 37 and 44 (amended claims filed 05/17/2010) of copending USSN 11/618,472, drawn to an anti-CD52 antibody comprising an Fc variant comprising modification 239D in the Fc region,

Claims 37 and 44 (amended claims filed 05/17/2010) of copending USSN 11/618,488, drawn to an anti-Her2/neu antibody comprising an Fc variant comprising modification 239D in the Fc region,

Claims 17 and 18 (amended claims filed 04/23/2010) of copending USSN 11/765,353, drawn to a protein comprising an Fc variant comprising amino acid substitution in position 239 including 239D in the Fc region, and

Claims 19-21 and 23-26 (amended claims filed 09/10/2009) of copending USSN 11/765,390, drawn to a protein comprising an Fc variant comprising amino acid substitution in position 239. The copending specification defines the protein as an antibody and substitution in position 239 encompasses 239D (e.g. see paragraphs [104] on page 26 and Table 4 on page 91 of the copending specification).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 88, 89, 103-106, 108, 109, 111, 112, 135-137, 139, 140, 142, and 144 are directed to an invention not patentably distinct from pending claims commonly assigned USSNs listed above for reasons stated, supra.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned USSNs, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

(10) Response to Argument

Appellant's arguments regarding the Restriction Requirement (mailed on July 26, 2006) have been fully considered but have not been found persuasive.

Appellant argues that according to MPEP 821.01, one may traverse an Examiner's holding that a given claim is not for elected subject matter and asserts that the holding is an appealable rejection (see 2nd full paragraph on page 21 of the Brief).

This argument is rendered moot for following reasons:

First of all, the Requirement for Restriction is a matter that is petitionable, not appealable (e.g. see MPEP 1201).

Second, appellant has elected the Group encompassing an antibody with 239D substitution without traverse on May 24, 2006. As such, appellant has lost the right to petition under 37 CFR 1.144.

Contrary to appellant's reliance on MPEP 821.01 for traversal of Restriction Requirement with the filing of the Brief, it is noted that MPEP 821.01 deals with issues related to election with traverse. Appellant is reminded that election must be made with traverse to preserve right of petition which is to be determined by the Technology Center Group Director. See MPEP 818.03 and 1201. Also note that petition of restriction requirement under 37 CFR 1.144 must be filed no later than Appeal. See MPEP 821.01.

In addition, similar petitions under 37 CFR 1.144 to request reconsideration of the restriction requirement in copending applications USSN 11/538,411 and 11/436,266 have been dismissed.

Therefore, appellant's arguments regarding the Restriction Requirement are render moot because judicial procedures have not been followed.

Response to Arguments to Rejection Under 35 U.S.C. 103(a) Against Claims 88, 89, 103-106, 108, 109, 111, 112, 135-137, 139, 140, 142, and 144 Based Upon Presta (US Patent 6,737,056)

Appellant's arguments in conjunction with various legal citations have been fully considered but have not been found convincing.

Appellant argues that in *Ex parte Watkins*, the Board of Patent Appeal and Interferences decided that the same prior art, Presta (US Patent 6,373,056), does not teach specific residues to be substituted in position 280. Thus, appellant argues that the Presta's disclosure of substituting the naturally occurring residue in position including 239 with any other naturally occurring amino acid residues does not constitute a description of substituting the amino acid at position 239 with any of the twenty amino acids.

The Examiner has no comment on the opinion in support of the decision with respect to *Ex Parte Watkins* because the opinion is not binding precedent of the Board.

However, *Ex parte Watkins* distinguishes from the instant application for following reasons:

The *Ex parte Watkins* deals with rejection under 35 U.S.C. 102(e), while the current rejection is under 35 U.S.C. 103(a). While the Board decided that Presta's disclosure of substituting the pre-existing amino acid residue in position 280 (while instant claims encompass position 239) with any other naturally occurring amino acid residues is not sufficient as anticipatory teachings, the Board has not decided whether Presta's teachings would render substitution in position 280 obvious. Further, the instant claims are not the same as the claims in *Ex parte Watkins*. Thus, the analysis in *Ex parte Watkins* would not be applicable here.

Furthermore, as an update, the prosecution for USSN 10/370,749 (the application in *Ex parte Watkins*) had been reopened and new ground of rejection under 35 U.S.C. 103(a) had been added. The case has since been abandoned.

Therefore, appellant's arguments relying upon the non-precedential opinion of *Ex parte Watkins* are not found persuasive.

Appellant argues that Presta only teaches a substitution of alanine (A) at position 239 as shown by the working example. Appellant acknowledges that Presta teaches position 239 of the Fc region of an antibody is involved in binding to the Fc gamma receptors (FcγRs) but asserts that Presta only discloses modification in position 239 for reduced binding to an FcγR. Appellant acknowledges that Presta's patented claim 13 does recite modification in position 239 of the Fc region with increased binding affinity to an FcγR but alleges that the functional limitation of "increased binding affinity to an FcγR" with respect to position 239 was not part of the original claims in Presta's Patent. Thus, appellant asserts that since claim 13 of Presta's Patent was not in the original claims, the teachings of Presta do not render the instant claims drawn to an antibody or immunoadhesin having increased binding affinity to an FcγR as a result of a substitution at position 239 of the Fc region.

This is not found persuasive for following reasons:

In contrast to appellant's reliance on the working examples and preferred embodiments of the prior art, it is noted that a prior art reference must be considered in its entirety, see MPEP 2141.02. Here the teachings of Presta with respect to position 239 of the Fc region, when considered in its entirety, encompasses embodiment broader than the working example of S239A.

Here, contrary to appellant's dismissal of the patented claim, it is noted that the claim 13 of the Presta explicitly claims a polypeptide comprising an variant Fc region having increased binding to an Fc gamma receptor wherein the polypeptide comprises amino acid modification in position 239 (see copy of Presta's claim 13 below)

> "13. A polypeptide comprising a variant Fc region which is not a native sequence Fc region and has increased binding to an Fc gamma receptor (Fc.gamma.R), which polypeptide comprises an amino acid modification at any one or more of amino acid positions 238, 239, 248, 249, 252, 254, 255, 256, 258,265, 267, 268, 269, 270, 272, 279, 280, 283, 285, 298, 289, 290, 292, 293, 294, 295, 296, 298, 301, 303, 305, 307, 312, 315, 324, 327, 329, 330, 335, 337, 338, 340, 360, 373, 376, 379, 382, 388, 389, 398, 414, 416, 419, 430, 434,435, 437, 438 or 439 of the Fc region, wherein the numbering of the residues in the Fc region is that of the EU index as in Kabat."

Given the clear recitation of the patented claim 13, it is reasonable to conclude that Presta teaches modification in position 239 of the Fc region with increased binding to an Fc gamma receptor.

Further, Presta provides clear teaching that position 239 of the Fc region of an antibody is the binding site for FcγR (Fc gamma receptor) (e.g. see lines 1-4 of the first full paragraph on column 3 of Presta). Presta further teaches that amino acid modification in position 239 of the Fc region would alter the binding of Fc to FcγR (e.g. see lines 1-5 of 5th paragraph on column 4 of Presta).

Furthermore, Presta provides guidance regarding amino acid substitutions using different naturally occurring residues. For example, Presta teaches that in addition to Ala (A), the preexisting residues in positions involved in FcγR binding (e.g. S239) can be substituted with any other amino acid residues (e.g. see last paragraph on column 19). Presta teaches that pre-existing neutral hydrophilic residues such as Ser (S) can be conservatively substituted with residues from the same group e.g. Thr (T) (e.g. see Table 1 on column 20) or non-conservatively substituted with amino acid residues with significant different side chain properties; for example, for pre-existing serine residues (belongs to neutral hydrophilic group), one can use Asp (D) or

Glu (E) (both belong to acidic group) or Gln (Q) (basic group) for non-conservative substitutions that would result in substantial modifications in the biological properties of the Fc region.

Therefore, the position 239 of the Fc region taught by Presta provides a point of intervention for altering the binding affinity to FcγR or efffector function of an antibody. Presta's teaching is enabling in the sense that it allows one of ordinary artisan to make Fc variants with S239 substituted to any other naturally occurring amino acid residue, preferably Threonine (T) (e.g. conservative S239T) and to select the Fc variants with increased affinity to FcγRs. A person of ordinary skill has good reason to pursue the known options, e.g. making conservative substitution of S239T or non conservative S239D (see column 12 and paragraphs between Tables in column 20 of Presta), within his or her technical grasp with reasonable expectation of success.

It appears that appellant argues that the increased binding to an FcγR for Fc variant with amino acid modification in position 239 recited in Presta's patented claim 13 was a new matter added during the prosecution of the prior art Patent.

Such arguments regarding the validity of a US Patent are not persuasive because a patent shall be presumed valid. Each claim of a patent (whether in independent, dependent, or multiple dependent form) shall be presumed valid independently of the validity of other claims. See 35 U.S.C. 282. In addition, the question of validity or invalidity is exclusively a matter to be determined by a court. See MPEP 1701.

In the present case, appellant argues position 239 was not originally claimed in Presta and thus tipped the balance of the obviousness analysis. However, appellant ignores the clear recitation of position 239 and limitation of increased binding affinity to an Fcγ receptor.

The selection of component of invention (e.g. S239T) is "obvious to try" because the problem addressed by invention (e.g. amino acid substitution at position 239 for increased binding affinity to an Fcγ receptor") is known, possible approaches to increase the binding of the Fc region to an Fcγ receptor via amino acid substitution in position 239 are known and finite.

For example, Presta teach that the only preferred substitution for pre-existing Serine (Ser) is Threonine (thr) (e.g. see Table 1 on column 20). Thus, substituting pre-existing serine in position 239 with threonine represents preferred and conservative substitution (e.g. see column 20 or see copy below).

"The substitution may, for example, be a "conservative substitution". Such conservative substitutions are shown in Table 1 under the heading of "preferred substitution".

Given that Presta specifically claims position 239 of the Fc region can be substituted for an Fc variant with increased binding to an Fc gamma receptor (FcγR) and Presta provides clear teachings of how to make amino acid substitution in position 239 with any other naturally occurring amino acid residues (including specific direction to Threonine for preferred substitution of Serine) and how to determine the binding affinity to Fc gamma receptors including FcRn, FcγRI, FcγRIIA, FcγRIIb, FcγRIIIA (e.g. see Table 6 on columns 57-58), one of skill in the art would be able to produce the Fc variants as claimed with increased binding affinity to an FcγR.

Moreover, appellant argues that the one of skill in the art would not select position 239 based upon Presta's working example of S239A in order to achieve better binding affinity of the Fc to FcγR because S239A substitution results in reduced binding affinity to FcγR. Appellant asserts there is no motivation to substitute pre-existing serine (S) in position 239 with the claimed amino acid residue aspartic acid (D), glutamic acid (E), glutamine (Q) or threonine (T) because different amino acid changes in the same position of the Fc region produces different results. For example, appellant argues that Presta shows S267A Fc variant exhibits increased binding to both FcγRII and FcγRIII but S267G has no binding to FcγRIII. Therefore, appellant argues that different amino acid substitutions have unpredictable outcomes.

This is not found persuasive for following reasons:

Contrary to appellant's reliance on the working example of S239A, it is noted that the key invention of Presta is not as narrow as the working example of S239A. Rather, the key invention of Presta is the identification of position S239 in the Fc region interacts with the Fc gamma receptors and can be substituted with other naturally occurring amino acid residues including conservative substitution with Threonine for increased binding for FcγR. Thus, Presta's teachings are not so limited to the working example of S239A as narrowly asserted by appellant. Rather, Presta teaches that position S239 in the Fc region can be substituted with other amino acid residues to increase the binding affinity of the Fc to an FcγR (e.g. see claim 13).

Contrary to appellant's arguments of unpredictability, it was well known in the art and expected that the twenty naturally occurring amino acid residues differ from each other in their chemical characteristics. For example, Presta teaches that in addition to Ala (A), the preexisting residues in positions involved in FcγR binding (e.g. S239) can be substituted with any other amino acid residues (e.g. see last paragraph on column 19). Presta teaches that pre-existing neutral hydrophilic residues such as Ser (S) can be conservatively substituted with residues from the same group e.g. Thr (T) (e.g. see Table 1 on column 20).

Further, Presta teaches non-conservative substitutions involving the use of amino acid residue with significant different side chain properties; for example, for Ser (belongs to neutral hydrophilic group) one can use Asp (D) or Glu (E) (both belong to acidic group) or Gln (Q) (basic group) for non-conservative substitutions that would result in substantial modifications in the biological properties of the Fc region.

Therefore, the expected difference with respect to the function of the Fc region resulted from substitutions of different amino acids residues constitutes predictable outcome to one of skill in the art.

A prior art reference may be considered to teach away when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the appellant." See *In re Gurley* , 31 USPQ2d 1130, 1131 (Fed. Cir. 1994).

Here in contrast to appellant's assertions that one of skill in the art would not pursue position 239 for increased binding to an Fc gamma receptor because S239A exhibits reduced binding to Fc gamma receptors; there is no discouragement nor skepticism in the prior art for substituting Serine in position 239 with other amino acid residues. In fact, Presta particularly points out that Threonine is the preferred substitution for Serine (e.g. see Table 1 on column 20).

"Teaching, suggestion, or motivation" test for obviousness of claimed invention should not be applied as rigid and mandatory formula, since it is necessary to show some articulated reasoning, with some rational underpinning, to support legal conclusion of obviousness, but such reasoning need not seek out precise teachings directed to specific subject matter of challenged claim". See *Aventis Pharma Deutschland GmbH v. Lupin Ltd.*, 84 USPQ2d 1197 (Fed. Cir. 2007)

In the present case, one of skill in the art would not disregard other amino acid substitutions, particularly the preferred Threonine, in position S239 simply because S239A yielded an Fc variant with reduced binding affinity to the FcγR. One of skill in the art would not be discouraged from testing other amino acid residues in position 239 even if Presta's working example S239A shows decreased binding to FcγR because position 239 is involved in binding to its receptors and substitution made in 239 clearly alters and can increase the binding affinity to FcγRs . A person of ordinary skill has good reason to pursue the known options (e.g. amino acid substitutions at position 239 of the Fc region) within his or her technical grasp. Even if the twenty amino acid residues cannot simply substituted one for another, such expected difference could not be equated with unpredictability or nonobviousness here because there were only a finite number of naturally occurring amino acid residues (nineteen, excluding the preexisting residues) and one for preferred conservative substitution for Serine (Threonine) to be tested in position 239 for altered affinity to the FcγRs. A person of ordinary skill in the art would have had a reasonable expectation that 239 variants within the claimed scope could have been successfully obtained.

Thus, the claimed conservative variant S239T or S239D, S239E, and S239Q are simply predictable variations.

In addition, appellant asserts that the Examiner dismissed the secondary indicia of non-obviousness filed on January 13, 2009 (See page 13 of the SUPPLEMENTAL REWARKS filed on January 14, 2009). Appellant argues that the claims are non-obvious over Presta because of the commercial success of the 239 variants by a number of companies.

This is not found persuasive for following reasons:

In contrast to appellant's assertion, it is noted that appellant has not provided objective evidence of commercial success. Further, there is a lack of establishment with regard to a nexus between the claimed invention and the evidence of commercial success. Appellant's mere assertion of commercial success does not establish a nexus between the claimed invention and

the commercial success because there is no evidence that the product has been sold and that said product corresponds to the claimed invention or whatever commercial success may have occurred is attributable to the antibody or immunoadhesin defined by the claims. See MPEP 716.03.

Given the examination guidelines for determining obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in *KSR International Co. v. Teleflex Inc*. 82 USPQ2d 1385 (2007) and the Examination Guidelines set forth in the Federal Register (Vol. 72, No. 195, October 10, 2007) and incorporated recently into the MPEP (Revision 6, September 2007), the following rationales to support rejection under 35 U.S.C. 103(a) are noted:

A) Combining prior art elements according to known methods to yield predictable results.

Appellant argues that the Examiner cannot note that the prior art shows unpredictability for the purpose of enablement and simultaneously argue that the prior art is predictable for the purpose of rejection under 35 U.S.C. 103(a).

This argument is rendered moot since the rejection on Appeal is under 335 U.S.C. 103(a), not enablement.

Here, the rationale to support a conclusion that the claims would have been obvious is that all the claimed elements (antibody or immunoadhesin comprising an Fc variant comprising amino acid substitutions S239D) were known in the prior art and one skilled in the art could have arrived at the claimed invention by using known methods (methods of making amino acid substitutions at position 239 and method of determining Fc-FcγR binding affinity taught by Presta, e.g. see Example 4 on columns 54-70) with no change in their respective functions and the combination would have yielded nothing more than predictable results of increased binding

to an FcγR of the antibody or immunoadhesin comprising an Fc variant compared to the parent antibody or immunoadhesin.

B) Simple substitution of one known element for another to obtain predictable results.

Appellant once again relying on *Ex parte Watkins* and asserts that the Board decided that Presta's definition of amino acid substitution which listed twenty naturally occurring amino acid residues does not describe substituting particular amino acid residues into specific position.

Appellant's arguments relying upon *Ex parte Watkins* have not been found persuasive for reasons stated above.

Further, appellant is reminded that the instant specification does not actually produce all the antibody variants encompassed in the instant claims. For example, the withdrawn claim 96 encompasses an antibody or immunoadhesin comprising amino acid substitutions at position 239 selected from the group consisting of 239D, 239E, and 239T, wherein the antibody or immunoadhesin further comprises an amino acid substitution selected from the laundry list of substitutions. Yet the instant specification does not actually provide working examples for all the variants encompassed in the instant claims.

Here, the rationale to support a conclusion that the claims would have been obvious is that the substitution of one known element (existing amino acid Ser (S) in position 239 of the Fc region) with another (Asp (D)), see claim 13, column 12 and paragraphs between Tables in column 20 of Presta) would have yielded predictable results of increased binding to an FcγR function to one of ordinary skill in the art at them time of the invention.

C) Use of known technique to improve similar products in the same way.

Appellant argues that there is no teaching, motivation or suggestion to try certain substitutions. Appellant asserts that Presta does not teach any 239 variants with increased binding to FcγR.

Appellant ignores the clear recitation of the claim in Presta's Patent (e.g. see claim 13). Further, Presta provides clear teachings, motivation, and suggestion for producing 239 variants for reasons stated above.

Here, the rationale to support a conclusion that the claims would have been obvious is that a method of enhancing a particular effector function (e.g. ADCC of an antibody) via increased binding affinity of Fc to an FcγR was made part of ordinary capabilities (e.g. amino acids substitution S239D of the Fc region, e.g. see claim 13 of Presta) of one skilled in the art based upon the teachings of Presta. One of ordinary skill in the art would have been capable of applying the known methods of amino acid substitution to make Fc variant S239D of an antibody or immunoadhesin to improve the effector function of the antibody including ADCC and the results would have been predictable to one of ordinary skill in the art.

D) Applying a known technique to a known product ready for improvement to yield predictable results.

The rationale to support a conclusion that the claims would have been obvious is that a particular known technique (amino acid substitution S239D of the Fc region of an antibody) was recognized as part of the ordinary capabilities of one skilled in the art. One of ordinary skill in the art would have been capable of applying this known technique to a known product (e.g. antibody or immunoadhesin) that was ready for improvement and the results would have been predictable to one of ordinary skill in the art.

E) "Obvious to try" --- choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success.

The rationale to support a conclusion that the claim would have been obvious is that a person of ordinary skill has good reason to pursue the known options (e.g. amino acid substitutions at position 239 of the Fc region) within his or her technical grasp. This leads to the anticipated success of increased binding of Fc to an FcγR and enhancement of ADCC effect of an antibody or immunoadhesin, it is likely the product not of innovation but of ordinary skill and common sense.

F) Some teachings, suggestion, or motivation in the prior art that would have lead one of ordinary skill to modify the prior art reference to arrive at the claimed invention.

Since the improvement of ADCC effect of an antibody with amino acid substitution at position 239 of the Fc region would have been predictable at the time of the invention, there would have been reasonable expectation of successful development of an antibody with improved ADCC effect as claimed. The prior art had recognized the obstacles to be overcome in development of antibody with improved ADCC effect, and had suggested a finite number of amino acid substitutions at position 239 of the Fc region to overcome this obstacles. The claims were obvious because it would have been obvious to try the known methods of amino acid substitutions at position 239 of the Fc region, with a reasonable expectation of success.

In this case, the position 239 of the Fc region taught by Presta provides a point of intervention for altering the efffector function of an antibody. A person of ordinary skill has good reason to pursue the known options, e.g. making S239D (see column 12 and paragraphs between Tables in column 20 of Presta), within his or her technical grasp with reasonable expectation of success.

"The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See *In re Rosselet*, 146 USPQ 183, 186 (CCPA 1965).

"There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." *Motorola, Inc. v. Interdiqital Tech. Corp.*, 43 USPQ2d 1481, 1489 (Fed. Cir. 1997).

An obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See *KSR Int'l Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.").

Given that the prior art goal was to improve ADCC effect of an antibody by substituting amino acid residues in position 239 of the Fc region, incorporating amino acid residue D in position 239 of the Fc region would have been routine to the ordinary artisan at the time the invention was made and therefore obvious in designing antibodies with improved ADCC effect as it reads on the claimed composition comprising an antibody variant.

In conclusion, given that the prior art teaches and claims that position 239 of the Fc region can be substituted for improved binding affinity to an FcγR, the prior art also provides multiple working examples of amino acids substitutions using naturally occurring amino acid residues in the Fc region, it would have been obvious to one of skill in the art at the time of the invention to achieve the predictable results of an antibody Fc variant with increased binding affinity to an FcγR for the enhancement of ADCC by making the claimed amino acid substitution in position S239 in the Fc region of an antibody or immunoadhesin.

Response to Arguments to Rejection of Provisional Obviousness-type Double Patenting Against Claims 88, 89, 103-106, 108, 109, 111, 112, 135-137, 139, 140, 142, and 144.

Appellant has not dispute that there are overlapping subject matters between the instant claims and the copending claims.

Appellant argues that the instant application was filed prior to any of the copending applications. Thus, appellant asserts that the according to MPEP 804, the rejection should be withdrawn.

This is not found persuasive for following reasons:

First, appellant's arguments reliance on MPEP 804 have not been found convincing because the obviousness-type double patenting rejection (ODP)is not the only rejection remaining in the instant application, see rejection under 35 U.S.C. 103(a) discussed above.

Second, appellant's interpretation regarding the definition of the "earlier filed application" is incorrect.

The term "earlier filed is to be determined as follows:

i) Where there is no benefit claim in the two (or more) applications, the "earlier filed" application is the one having the earlier actual filing date.

ii) Where at least one of the two (or more) applications is entitled to the benefit of a US nonprovisonal application under 35 U.S.C. 120 or 121, or of an international application under 35 U.S.C. 120, 121, or 365(c); the "earlier filed" application is the one having the earlier effective US filing date, taking into account of each 35 U.S.C. 120, 121, and 365(c).

Here, the instant application does not claim benefit to a US nonprovisonal application under 35 U.S.C. 120 or 121. As such, the date relied upon herein for the instant application is the actual filing date of 09/26/2003.

For the copending applications, for example, the copending USSN 11/124,620 claims benefit to several nonprovisional USSNs, among which the one having the earlier effecting US filing date is the instant application filed 09/26/2003 (the '620 copending application is a continuation-in-part of the instant application).

As such, the instant application and the copending application have the same effective filing date, in turn, the instant application is not "an earlier filed application". Therefore, a terminal disclaimer is requried to overcome the rejection even if the "provisional" ODP is the only rejecton remaining.

Further, a showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

Therefore, appellant's arguments have not been found persuasive.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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Examiner, Art Unit 1644

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/Ram R. Shukla/
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